REMARKS

Claims were 16, 18, and 20-25 were pending in the application. Claims 16, 18, 20, 23, 24, and 25 have been canceled, without prejudice, and claim 22 has been amended. New claims 30 and 31 have been added. Accordingly, after the amendments presented herein have been entered, claims 22, 30 and 31 will be pending in the instant application. For the Examiner's convenience, the pending claims are set forth in Appendix A.

Applicants submit herewith a "Version with Markings to Show Changes Made," which indicates the specific amendments made to the specification and the claims. *No new matter has been added.*

Support for the amendments to claim 22 and new claims 30 and 31 can be found throughout the specification and claims as originally filed.

Any amendments to the claims are not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Objections to the Specification

The Examiner is has objected to the amendment filed 3/26/02 under 35 U.S.C. 132 because "it introduces new matter into the disclosure." In particular, the Examiner is of the opinion that

> The file labeled "Table 2.txt" and referred to as Table 2 apparently contains structural coordinates for $cPLA_2$. The originally filed specification did not contain a "Table 2" or structural coordinates for cPLA2 in any other format; e.g. as a Figure, Addendum or other attachment. No CD-R was filed with or incorporated by reference into the original specification. Applicant states on page 5 of the response filed 3/26/02 that the structural coordinates found in "Table 2.txt" were deposited in the Brookhaven Protein Databank (BPD) as accession number 1CJY and is referred to on page 41 of the amended specification and is incorporated by reference on page 54 of the amended specification. However, page 39 of the *originally filed* specification states that "Coordinates *will be* deposited at the Brookhaven Protein Databank" (emphasis

> added by examiner) and does not incorporate crystal coordinates (or Table 2) by reference anywhere. The PDB record (accession number 1CJY) indicates that crystal coordinates were deposited on April 20, 1999, which is AFTER the filing date of the instant application. The article cited by the PDB was issued by Cell (IDS ref. Dessen et al. Cell. vol. 39, pp. 349-360) on April 30, 1999, again AFTER the filing date of the instant application. As the crystal coordinates were not deposited or otherwise made publicly available until AFTER the filing date of the instant application, it is unlikely that the crystal coordinates contained in Table 2 were incorporated by reference from either the PDB or another publication in the originally filed specification. The originally filed specification did not disclose crystal coordinates corresponding to Table 2 anywhere. The originally filed claims did not recite the crystal coordinates of Table *2.*

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution of the foregoing objection, and in no way acquiescing to the Examiner's objection, Applicants have amended the specification to remove Table 2 containing the structural coordinates for $cPLA_2$, and all references to Table 2. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the specification.

Furthermore, the Examiner is also of the opinion that

> The newly amended specification refers to SEQ ID NO's 2 and 3. The amendment of 7/27/00 added new pages 53-56 which were the paper sequence listing identifying SEQ ID NO's 1 and 2. SEQ ID NO: 2 was disclosed in the originally filed specification on page 4, and thus was not new matter. The entirety of SEQ ID NO: 1 was not specifically disclosed by the originally filed specification; however, the originally filed specification taught on page 6, lines 1-5, a $cPLA_2$ sequence found in Table 1 of US Patent 5,527,698. The specification was amended to state that the $cPLA_2$ sequence was found in SEQ ID NO: 1 and in Table 1 of US Patent 5,527,698. As the amended specification disclosed that the sequence in Table 1 of US Patent 5,527,698 is the same as SEQ ID NO: 1, SEQ ID NO: 1 is not considered new matter. Applicant is advised that if SEQ ID NO: 1 of the sequence listing is not identical to that taught in Table 1 of US Patent 5,527,698, then SEQ ID NO: 1 is considered new matter.

Applicants respectfully submit that SEQ ID NO:1 of the Sequence Listing is identical to that taught in Table 1 of U.S. Patent No. 5,527,698. Accordingly, SEQ ID NO:1 is not new matter. Therefore, Applicants respectfully request withdrawal of the foregoing objection as it pertains to SEQ ID NO:1.

The Examiner is further of the opinion that

> Neither the originally filed specification nor the sequence listing teach a SEQ ID NO: 3 or identify a sequence corresponding to a SEQ ID NO: 3. The pentapeptide which corresponds to SEQ ID NO: 2 of the sequence listing is now labeled SEQ ID NO: 3 on page 4 of the substitute specification filed 3/26/02, and the polypeptide sequence labeled SEQ ID NO: 1 of the sequence listing now appears to be labeled as SEQ ID NO: 2 throughout the newly amended specification. The examiner has not been able to find a sequence labeled "SEQ ID NO: 1" in the amended specification. If applicant intends to disclose SEQ ID NO's 2 and 3, then the new sequence (SEQ ID NO: 1?) is new matter. Further, if there are three sequences, then the specification fails to comply with the sequence rules. Applicant is reminded that sequence numbers must start at 1 and be sequential (i.e. there must be a SEQ ID NO: 1). Applicant is further reminded that sequences must be listed in the sequence listing AND in a CRF, and that the sequence listing and CRF must be identical. The instant sequence listing and CRF contain only SEQ ID NO's 1 and 2. The substitute specification filed 3/26/02 does not contain sequence listing pages, but does contain "substitute" pages numbered through p. 55. As applicant has not specifically deleted the sequence listing pages, it is assumed that the prior sequence listing pages (pp. 53-56, as filed 7/27/00) are not amended or deleted, and the sequence listing page numbers will be changed to pp. 56-59, respectively.
> It is possible that the "new" SEQ ID NO's are merely a typographical error. If so, this objection may be overcome by amending the specification to disclose the correct SEQ ID NO's (i.e. SEQ ID NO's 1 and 2). Applicant is reminded that the substitute specification filed 9/5/00, which included substitute sequence listing pages, was not entered.

Applicants respectfully traverse the foregoing objection to the specification. However, in an effort to expedite prosecution of the instant application, Applicants respectfully submit that a Substitute Sequence Listing (pages 55-61) which includes SEQ

ID NOs:1, 2, and 3 is being filed concurrently herewith. Furthermore, Applicant submits concurrently herewith to Box Sequence Listing a Diskette containing substitute computer readable form (CRF) of the Substitute Sequence Listing for the above-referenced patent application, and a separate transmittal letter for the Diskette.

The Substitute Sequence Listing being filed herewith corresponds to the substitute specification (pages 1-54) filed on March 22, 2002. The pentapeptide labeled SEQ ID NO:3 on page 4 of the substitute specification filed on March 22, 2002 corresponds with SEQ ID NO:3 of the Substitute Sequence Listing. Furthermore, SEQ ID NO:1 represents the nucleotide sequence which encodes the amino acid sequence of SEQ ID NO:2. The specification has been amended to refer to SEQ ID NO:1 as well as SEQ ID NO:2. *No new matter has been added.* Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to the specification.

Rejection of Claims 16, 18, and 20-25 Under 35 U.S.C. §112, first paragraph

The Examiner has stated that "[i]n view of the amendment to the specification (Table 2), which discloses crystallographic coordinates for $cPLA_2$, the rejection of claims 16, 18, and 20-25 under 35 USC 112, first paragraph, with regard to enablement due to lack a pure and/or crystallized molecule, is hereby withdrawn. Applicant is advised, however, that Table 2 is considered new matter, as set forth above; cancellation of Table 2 may result in reinstatement of the enablement rejection."

Applicants respectfully submit that the specification has been amended to delete Table 2. Applicants also respectfully submit that claims 16, 18, 20, 23, 24, and 25 have been canceled, thereby rendering any rejection of these claims moot. Applicants respectfully submit that should the aforementioned rejection be reinstated, claim 22, as amended, is fully enabled by Applicants' specification. One of ordinary skill in the art would be able to identify, based on the atoms of the amino acids disclosed in Applicants' specification which are involved in binding, inhibitors which are known to block the active site. Applicants' specification describes the structure of the $cPLA_2$ molecule including the structure of the active site. The active site of the cPLA2 molecule is described in detail in Applicants' specification (see, for example, page 14, line 3 through

page 24, line 26 of the specification). For example, at page 19, lines 10-17, Applicants' specification describes the active site funnel and the location of Ser228 and Asp549 relative to the active site funnel. The diameter of the funnel as well as the fact that the funnel is lined with hydrophobic residues is also described. The active site is further described in Applicants' specification at, for example, page 21, line 20 through page 23, line 9. Furthermore, one of ordinary skill in the art would be able to recognize which specific chemical entity binds to the atoms of the amino acids listed in claim 22, *e.g.,* CB and Oγ atoms of Ser228. Based on the details regarding the location, size, and configuration of the catalytic domain of $cPLA_2$ and the amino acids contained within the catalytic domain as described in Applicants' specification, one of skill in the art would be able identify inhibitors of $cPLA_2$ without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 20, 22, 23, and 25 Under 35 U.S.C. §112, first paragraph

The Examiner has also rejected claims 20, 22, 23 and 25 under 35 U.S.C. 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." In particular, the Examiner is of the opinion that "Applicant has not set forth any arguments with regard to lack of a teaching for how to synthesize putative inhibitors or with regard to lack of a teaching for how to determine atoms or amino acids involved in catalysis; nor has an amendment been filed which overcomes the rejection, therefore the rejection of claims 20, 22, 23, and 25 is maintained."

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection, claims 20, 23, and 25 have been canceled, without prejudice, thereby rendering the foregoing rejection moot as it pertains to these claims.

With respect to claim 22, Applicants respectfully submit that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation for the following reasons. Claim 22, as amended, requires ***providing*** a

potential inhibitor that will form non-covalent bonds with one or more amino acids in the $cPLA_2$ active site and determining whether the potential inhibitor inhibits the activity of $cPLA_2$. Synthesis of potential inhibitors is no longer required by the claims.

Furthermore, with respect to claim 22, as amended, Applicants respectfully submit that one of skill in the art would be able to determine atoms or amino acids involved in catalysis based on Applicants' specification. All of the atoms of the amino acids listed in claim 22 are part of the $cPLA_2$ active site (see, for example, Applicants' specification at page 8, line 4 through page 9, line 2). Furthermore, Applicants' specification describes the structure of the $cPLA_2$ molecule including the structure of the active site. The active site of the cPLA2 molecule as well as the amino acids involved in catalysis are described in detail in Applicants' specification (see, for example, page 14, line 3 through page 24, line 26 of the specification). Based on the details regarding the location, size, and configuration of the catalytic domain of $cPLA_2$ and the amino acids contained within the catalytic domain as described in Applicants' specification, one of skill in the art would be able to recognize atoms or amino acids involved in catalysis without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claim 18 Under 35 U.S.C. §112, first paragraph

The Examiner has also rejected claim 18 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

In particular, the Examiner is of the opinion that

> [c]laim 18 recites a step of determining the interaction between a candidate substance and a model of the structure of cPLA2. A model, according to Merriam-Webster's dictionary, is an imitation or emulation; i.e. a model is not the thing itself. The specification does not disclose how to determine the interaction of an emulation of the structure of $cPLA_2$ with a candidate substance. In the instant case, based on the teachings of the specification, the examiner interprets a "model of the structure of $cPLA_2$" to be a computer

> representation (3D emulation of crystal coordinates or data set representing a spatial arrangement of atoms). A "substance" is interpreted to be an actual compound, not a data set or 3D computer emulation.

Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution of the instant application and in no way acquiescing to the instant rejection, Applicants have canceled claim 18, without prejudice. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 23 and 25 Under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 23 and 25 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

In particular, the Examiner is of the opinion that

> [n]either an electrostatic patch region nor ANY region comprising amino acids Arg467, Arg485, Lys488, Lys544, and/or Lys543 is described by the instant specification....The amended specification discloses on page 15, lines 4-16, a highly basic region which would be expected of a region making multiple electrostatic contacts. The specification also discloses on page 15, lines 9-11 that it is "impossible to accurately define the true size of the basic patch." The specification further discloses on page 18 that the highly basic region is *hypothesized* as making electrostatic contacts. The basic patch of pages 15 and 18 is not disclosed as one which is KNOWN to be an electrostatic region. Yet further, the basic patch disclosed on pages 15 and 18 is not specifically defined by the specification. That is, the patch is discussed in "regional" terms on page 15, but the area or length of the patch is not disclosed anywhere, and in fact, the specification discloses on page 15 that the true size of the patch is impossible to determine. Thus, the specification fails to specifically disclose an electrostatic patch region in $cPLA_2$. The specification does not disclose that the basic patch or any other region comprises Arg467, Arg485, Lys488, Lys544, and/or Lys543. Figure 2C discloses Arg 57 and Arg59, but these do not appear to be in the region hypothesized to be the "basic patch".

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection, claims 23 and 25 have been canceled, without prejudice, thereby rendering the foregoing rejection moot as it pertains to these claims.

Rejection of Claims 16, 18, and 20-25 Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 16, 18, and 20-25 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, the Examiner is of the opinion that

> [c]laim 20 recites the phrase "the crystal structure co-ordinates of $cPLA_2$" in lines 4-5. There is no antecedent basis for this term in the claims, therefore the claim is indefinite. Claim 20 recites a step (c) of "determining whether the potential inhibitor inhibits the activity of cPLA2". Claim 20 does not recite any specific steps for carrying out the determination of step (c). Many methods are known in the art for "determining" if a compound is an inhibitor of a particular activity, therefore the claim is enabled. However, as it is unclear what method steps applicant intends for his "determination", and it is unclear what "activity" is to be inhibited (*e.g.* lipid binding only, transmembrane movement, catalysis, etc.), one skilled in the art would not know the metes and bounds of applicant's inventive method, and the claim is indefinite.

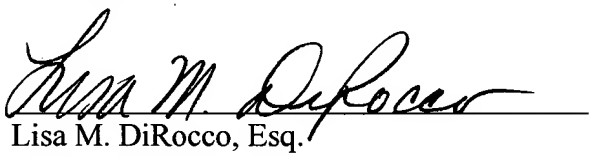
Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution of the instant application and in no way acquiescing to the instant rejection, Applicants have canceled claims 16, 18, 20, 23, 24, and 25, without prejudice. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection with respect to these claims.

With respect to claim 22, Applicants respectfully submit that claim 22 now includes the limitations of claim 20. Applicants respectfully submit that claim 22, as amended, particularly points out and distinctly claims the subject matter of Applicants' invention. Applicants respectfully submit that the phrase "determining whether the potential inhibitor inhibits the activity of $cPLA_2$" is clear and definite. Based on the plain language of the claim, it would be clear to one of skill in the relevant art that this phrase is directed to determining, ***by any method possible***, whether the potential inhibitor inhibits the activity of $cPLA_2$. As stated by the Examiner, many methods are known in the art for determining modulation of activity of cPLA2. Furthermore, the specification describes several assays which may be utilized to determine modulation of activity of $cPLA_2$ (see Example 2, pages 41-44 of Applicants' specification). With respect to the particular activity to be inhibited, Applicants respectfully submit that based on the plain language of the claim, one of ordinary skill in the relevant art would understand that any $cPLA_2$ activity may be inhibited by the identified inhibitors. As indicated by the Examiner, many $cPLA_2$ activities are known in the art. "Breadth of a claim is not to be equated with indefiniteness *In re Miller,* 441 F.2d 689, 169 USPQ 597 (CCPA) 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph." (MPEP 2173.04). Applicants respectfully submit that the subject matter of claim 22 is clear and definite. Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing 35 U.S.C. §112, second paragraph rejection.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Dated: **January 10, 2003**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please delete the Substitute Sequence Listing contained on pages 53-56 of the specification as filed July 27, 2000, and replace it with the new Substitute Sequence Listing, filed herewith (pages 55-61).

Please delete Table 2, which was submitted as an electronic file named "Table 2.txt" on March 22, 2002.

Please delete the paragraph beginning at page 1, line 1.

Please amend the paragraph beginning at page 6, line 2 as follows:

--All references to amino acids in cPLA2 herein are made using residue numbers which refer to the cPLA2 sequence found in SEQ ID NO:2 and in Table I of U.S. Patent No. 5,527,698, with the first methionine being designated residue 1 (Met1). SEQ ID NO:2 is encoded by the nucleotide sequence set forth in SEQ ID NO:1.--

Please amend the paragraph beginning at page 41, line 13 as follows:

--Coordinates will be deposited at the Brookhaven Protein Databank~~, and are included in Table 2~~.--

In the claims:

Please cancel claims 16, 18, 20, 23, 24, and 25, without prejudice, and amend claim 22 as follows:

22. **(Amended)** ~~The method of claim 20~~ A method of identifying inhibitors of $cPLA_2$ activity comprising:

(a) providing a potential; and

(b) determining whether the potential inhibitor inhibits the activity of $cPLA_2$, wherein said inhibitor ~~is designed to~~ interacts with one or more atoms of said one or more amino acids in the $cPLA_2$ active site, and wherein said one or more atoms is selected from the group consisting of:

CB and Oγ atoms of Ser228;

Oδ1and Oδ2 atoms of Asp549 and Asp575;

CB, CG, CD, NE, CZ, NH1 and NH2 atoms of Arg200, Arg413 and Arg579;

Backbone carbonyl oxygen of Trp393;

Nδ2 and Oδ1 atoms of Asn555;

Atoms CD1, CE1, CG, CZ, CE2, and CD2 of Phe397, Phe681, Phe683 and Phe199;

CG, CD1, NE1, CE2, CZ2, CH2, CZ3, CE3 and CD2 of Trp232 and Trp393;

CB and Oγ atoms of Ser577;

Atom s CB and Sγ of Cys331;

Atoms OE1 and OE2 of Glu589;

Atoms CB, CG, CD, CE and NZ of Lys588;

Oγ1 atom of Thr680;

OE1 and OE2 atoms of Glu418 and Glu422;

Atoms CB, CG, SD and CE of Met417;

Atoms CB, CG, CD1 and CD2 of Leu400 and Leu421;

Atoms CB, CG1, CG2, or CD1 of Ile424;

Backbone NH and carbonyl oxygen atoms of Ala578; and

Atoms CB, CG, ND1, CE1, NE2, and CD2 of His639.

Please add new claims 30 and 31 as follows:

30. **(New)** The method of claim 22, wherein said activity of $cPLA_2$ is lipid binding.

31. **(New)** The method of claim 22, wherein said activity of $cPLA_2$ is membrane binding.

APPENDIX A

22. A method of identifying inhibitors of $cPLA_2$ activity comprising:

(a) providing a potential inhibitor; and

(b) determining whether the potential inhibitor inhibits the activity of $cPLA_2$, wherein said inhibitor interacts with one or more atoms of said one or more amino acids in the $cPLA_2$ active site, and wherein said one or more atoms is selected from the group consisting of:

CB and Oγ atoms of Ser228;

Oδ1and Oδ2 atoms of Asp549 and Asp575;

CB, CG, CD, NE, CZ, NH1 and NH2 atoms of Arg200, Arg413 and Arg579;

Backbone carbonyl oxygen of Trp393;

Nδ2 and Oδ1 atoms of Asn555;

Atoms CD1, CE1, CG, CZ, CE2, and CD2 of Phe397, Phe681, Phe683 and Phe199;

CG, CD1, NE1, CE2, CZ2, CH2, CZ3, CE3 and CD2 of Trp232 and Trp393;

CB and Oγ atoms of Ser577;

Atom s CB and Sγ of Cys331;

Atoms OE1 and OE2 of Glu589;

Atoms CB, CG, CD, CE and NZ of Lys588;

Oγ1 atom of Thr680;

OE1 and OE2 atoms of Glu418 and Glu422;

Atoms CB, CG, SD and CE of Met417;

Atoms CB, CG, CD1 and CD2 of Leu400 and Leu421;

Atoms CB, CG1, CG2, or CD1 of Ile424;

Backbone NH and carbonyl oxygen atoms of Ala578; and

Atoms CB, CG, ND1, CE1, NE2, and CD2 of His639.

30. The method of claim 22, wherein said activity of $cPLA_2$ is lipid binding.

31. The method of claim 22, wherein said activity of $cPLA_2$ is membrane binding.